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Review

Fumonisins: Toxicokinetics, mechanism of action and toxicity

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Abstract

Fumonisins are mycotoxins produced by *Fusarium verticillioides* and *F. proliferatum*. They occur worldwide and are found predominantly in maize and in maize-based animal feeds. Of the fumonisins, fumonisin B_1 (FB_1) is the most common and the most thoroughly studied. FB_1 causes the same toxicities in animals as *F. verticillioides*- and *F. proliferatum*-contaminated feeds including equine leukoencephalomalacia (ELEM) and porcine pulmonary edema (PPE), diseases long associated with the consumption of mouldy feed by horses and pigs, respectively. FB_1 is toxic to the liver in all species and the kidney in a range of laboratory and farm animal species, causing apoptosis followed by mitosis in the affected tissues. FB_1 is also toxic to the cardiovascular system in pigs and horses. FB_1 and other fumonisins inhibit ceramide synthase in all species including laboratory and farm animals and disrupt sphingolipid metabolism, a process underlying the mechanism of toxicity and pathogenesis of fumonisin-related diseases. The USFDA has set guidances for fumonisin concentrations in animal feeds that range from 1 to 50 ppm in the formulated rations depending upon the animal species. The European Union Commission has recommended guidance levels for fumonisins B_1 plus B_2 in feed materials and formulated feedstuffs. The levels also vary according to species and range from 5 ppm for horses, pigs, rabbits and pet animals to 50 ppm for adult ruminants and mink. Awareness of fumonisin-related animal diseases, monitoring feed and feed components, and adherence to guidance

Abbreviations: AUC, area under the curve; CSL, complex sphingolipids; FB_1, fumonisin B_1; ELEM, equine leukoencephalomalacia; HFB, hydrolyzed fumonisin; PPE, porcine pulmonary edema; Sa, sphinganine; So, sphingosine; TCA, tricarballylic acid; USFDA, United States Food and Drug Administration

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recommendations are important for reducing fumonisin-induced diseases in agriculturally important species.

Keywords: Fumonisins; Equine leukoencephalomalacia; Porcine pulmonary edema; Toxicity; Mechanism of action; Bioavailability

Contents

1. Introduction

Fumonisins are produced by *Fusarium verticillioides* (formerly = *F. moniliforme*), *F. proliferatum*, and other *Fusarium* species (Gelderblom et al., 1988; Bolger et al., 2001; Glenn, 2007). While these mycotoxins are found in other commodities (da Silva et al., 2000; Seefelder et al., 2002; Kritzinger et al., 2003; Binder et al., 2007), animal and human health problems related to these mycotoxins are almost exclusively associated with the consumption of contaminated maize or products made from maize (Bolger et al., 2001; Marasas, 2001). The human health effects of fumonisins are uncertain. However fumonisins are suspected risk factors for esophageal (Marasas, 2001) and liver (Ueno et al., 1997) cancers, neural tube defects (Gelineau-van Waes et al., 2005; Missmer et al., 2006), and cardiovascular problems (Fincham et al., 1992) in populations consuming relatively large amounts of food made with contaminated maize.

While causality between fumonisins and human disease is unproven, this is not the case for animals. Consumption of moldy maize has long been a recognized cause of equine leukoencephalomalacia (ELEM) and, over the years, experiments have demonstrated that *F. verticillioides*-contaminated feeds and fumonisin B_1 (FB_1) can induce ELEM (Kellerman et al., 1990). Similarly, *F. verticillioides*-contaminated feeds and FB_1 have been shown to be cardiotoxic and cause pulmonary edema in pigs, a syndrome termed porcine pulmonary edema or PPE (Harrison et al., 1990; reviewed by Haschek et al., 2001). Cattle and poultry are considerably less sensitive to fumonisins than horses, pigs, rabbits, or laboratory rodents (reviewed in Bolger et al., 2001). The USFDA Center for Food Safety and Nutrition has issued guidance levels for fumonisins in maize and maize-byproducts used in animal feeds (Center for Food Safety and Nutrition, 2001). The levels vary by species, reflecting their relative sensitivities to fumonisins (Table 1). The European Union (Commission of European Communities) has also recommended guidance levels for fumonisins in animal feed materials and formulated feeds (Table 2). Like the FDA guidances, the European Union recommendations vary according to species. An overview of the fumonisins, their bioavail-

Table 1
FDA guidance levels for total fumonisins ($FB_1 + FB_2 + FB_3$) in animal feed[a]

Species	Feed factor[b]	Total fumonisins (ppm)	
		Maize or maize byproduct in formulated feed	Formulated feed
Horses/other *Equidae*	0.2	5[c]	1
Rabbits	0.2	5	1
Canines/felines/all other[d]	0.5	10	5
Catfish	0.5	20	10
Pigs	0.5	20	10
Ruminants[e]			
Lactating dairy cows	0.5	30	15
Breeding stock	0.5	30	15
For slaughter[f]	0.5	60	30
Mink	0.5	60	30
Poultry[g]			
Layers	0.5	30	15
Breeders	0.5	30	15
For slaughter	0.5	100	50

[a] Adopted from Center for Food Safety and Nutrition (2001).
[b] Percent of formulated ration composed of maize or maize byproduct.
[c] Maize screenings not to be included in rations for *Equidae*.
[d] Other species not listed in table.
[e] Includes beef cattle, sheep, goats and other ruminants.
[f] Animals $\geq$3 months of age.
[g] Includes chickens, turkeys, ducklings and other poultry species.

Table 2
European Union Commission recommendations for fumonisins B_1 (FB_1) + B_2 (FB_2) in products intended for animal feed[a]

$FB_1 + FB_2$[b,c] (ppm)	Species
5	Horses and other *Equidae*, pigs, rabbits, pet species
10	Fish
20	Lambs, kids, calves (<4 months of age), poultry species
50	Ruminants (adult) and mink

[a] Adapted from Commission of European Communities (2006).
[b] Values pertain to complementary and complete feedstuffs and are relative to products having 12% moisture content.
[c] Guidance for maize and maize product materials for feed is 60 ppm and includes non-cereal materials such as roughages and forages; daily exposure to $FB_1 + FB_2$ through direct feeding of these materials should not exceed those that would occur through completed rations containing the indicated level of fumonisins.

ability, toxicology, and other considerations contributing to establishment of the guidance levels follows.

2. Chemical structure

The chemical structure of the fumonisins was first reported in 1988 (Gelderblom et al., 1988) (Fig. 1). For more information on the chemistry and analytical methods for fumonisins see Krska et al. (2007). Since then, more than 28 homologues have been discovered and more are likely to be found (Rheeder et al., 2002; Humpf and Voss, 2004). FB_1 is the most common and, from a toxicological standpoint, the most thoroughly studied. FB_2, FB_3 and FB_4 are in order less prevalent and differ structurally from FB_1 in the number and placement of hydroxyl groups on the molecule's hydrocarbon "backbone". The structural similarity of fumonisins to the sphingoid bases sphinganine (Sa) and sphingosine (So) is critical to their ability to disrupt sphingolipid metabolism (Merrill et al., 2001; Riley et al., 2001), as discussed below.

When cooked under alkaline conditions (nixtamalization), as when maize is made into masa for tortillas and other foods (Humpf and Voss, 2004 and references therein), the tricarballylic acid (TCA) groups are cleaved, yielding a corresponding hydrolyzed FB_1 (HFB_1), HFB_2, HFB_3, *etc.* (also known as aminopolyols; Merrill et al., 2001), which have been found in alkaline cooked products (Voss et al., 2006a). Partially hydrolyzed fumonisins, that is, those lacking one TCA group, have also been found in the faeces of rats (Frank Ross, personal communication) and nonhuman primates (Shephard et al., 1994); while the mechanism of their formation is not well understood, it is likely carried out by gut microflora. The health effects of partially or fully hydrolyzed fumonisins to agriculturally important species has not been established but is likely not significant. This expectation is based on the low amounts of these compounds found in maize (Voss et al., 2006a) and their comparatively (relative to FB_1) low biological activity and toxicity *in vivo* (Gelderblom et al., 1996; Howard et al., 2002).

Fumonisin's primary amine function appears necessary for its biological activity. *N*-Substituted fumonisins such as *N*-acetyl FB_1, *N*-carboxymethyl FB_1 ($NCFB_1$), or fumonisin

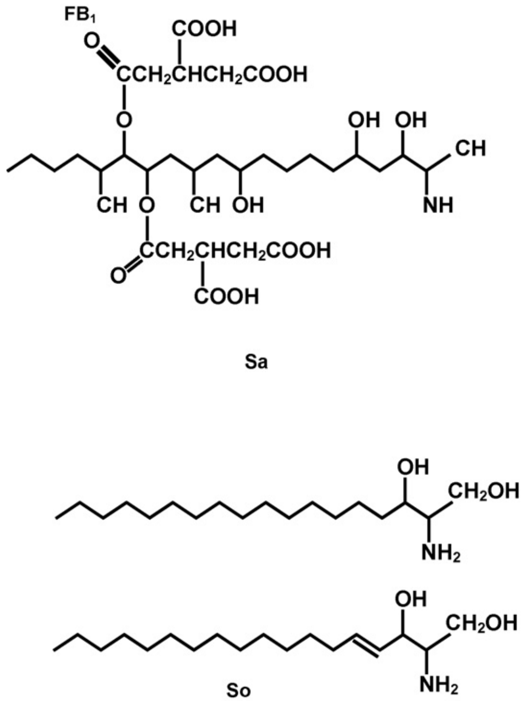

Fig. 1. Chemical structure of fumonisin B_1 (FB_1) which has similar structure to the sphingoid bases, sphinganine (Sa) and sphingosine (So). FB_2 differs from FB_1 only by the absence of the hydroxyl group at C10, FB_3 differs from FB_1 by the absence of the hydroxyl group at C5, and FB_4 lacks both the C5 and the C10 hydroxyl groups. More detailed information on the chemical structure of fumonisin compounds is available in the review by Humpf and Voss (2004) and Krska et al. (2007).

P_1 failed to elicit effects in experiments carried out both *in vivo* (Howard et al., 2002; Fernandez-Surumay et al., 2005) and *in vitro* (Norred et al., 2001). Furthermore, deamination of FB_1 with sodium nitrite effectively reduced its toxicity to *Hydra attenuata* (Lemke et al., 2001).

3. Biodistribution and pharmacokinetics

3.1. Laboratory animals

The results of biodistribution studies in rodents and nonhuman primates indicate that FB_1 and FB_2 are poorly absorbed from the gastrointestinal tract, rapidly cleared from the blood and that little fumonisin accumulates in the tissues, although low amounts are found in the liver and kidney (Norred et al., 1993; Shephard et al., 1995; Shephard and Snijman, 1999; reviewed by Voss et al., 2001; Riley and Voss, 2006). The pharmacokinetic study of Martinez-Larranaga et al. (1999) corroborated these findings. Absorption of orally administered FB_1 (10 mg/kg body weight) by rats was low (3.5% of dose) but rapid (T_{max} = 1.02 h), with the maximum plasma concentration (C_{max}) being 0.18 μg/ml. Plasma distribution of the absorbed dose conformed to a two-compartment open model and the tissue concentration time results were consistent with a one-compartment open model. Elimination half-lives were 3.15 h for plasma, 4.07 h for liver, and 7.07 h for kidney. FB_1 accumulated in the liver and kidney; the respective $AUC_{tissue}/AUC_{plasma}$ (AUC = area under the concentration–time curve) ratios were 2.03 and 29.9, indicating that FB_1 accumulates in the kidney to a greater extent than in liver. In another study, HPLC-mass spectrometric measurements indicated the presence of fumonisins in the liver and kidney of rats fed diets containing fumonisins for 3 weeks; concentrations in the kidney were approximately 10-fold higher than in the liver (Riley and Voss, 2006).

3.2. Pigs

Results of biodistribution and pharmacokinetic studies in pigs by Prelusky et al. (1994, 1996a) indicated a similar pattern of rapid absorption, rapid elimination, and low tissue residues. After intravenous (i.v.) administration of 0.4 mg/kg body weight [^{14}C]FB_1 (0.25 μCi), elimination from the plasma was tri-exponential. The respective half-lives for the initial (α)-, distribution (β)- and the terminal elimination (γ)-phases were $t_{1/2\,\alpha}$ = 2.2 min, $t_{1/2\,\beta}$ = 10.5 min and $t_{1/2\,\gamma}$ = 182 min and less than 0.02 of the peak FB_1 concentration remained in the plasma after 30 min. Recovery from urine plus plasma ranged from 0.76 to 0.83 of the dose after 72 h, at which time about 0.20 of the radioactivity remained in the tissues. In bile duct cannulated pigs (Prelusky et al., 1994) given FB_1 i.v., the radiolabel was cleared from blood more rapidly. In this case, elimination kinetics fit a two-compartmental model with $t_{1/2\,\alpha}$ = 3.6 min and $t_{1/2\,\beta}$ = 17.1 min. Most of the radioactivity (0.84–0.94 of the dose) was recovered from bile, urine and feces within 72 h, and the majority of this amount was found in the bile (0.67–0.75 of the dose). Recovery from the tissues averaged about 0.12 of the dose; the highest specific activities (still representing a low percentage of the dose) were found in the liver and kidneys.

Following intragastric dosing (0.35 μCi [^{14}C]FB_1 in 0.5 mg/kg body weight) (Prelusky et al., 1994), the radiolabel appeared in the blood after 30 min and most was eliminated in the faeces (0.87–0.95 of the dose) within 72 h. On average, less than 0.005 of the dose was excreted in urine. The calculated bioavailability of the mycotoxin was approximately 0.041 of the dose (Prelusky et al., 1996b). Intragastric doses were also given to bile duct cannulated animals and, in this case, recovery from plasma, urine and feces after 72 h ranged from 0.87 to 0.95. Most (0.86–0.94 of the dose) of the recovered radioactivity was found in the faeces. Small amounts of radiolabel were recovered from the bile (≤0.017 of dose) and urine (≤0.012 of dose) and the specific activities in the tissues of the orally dosed pigs were low, with the highest specific activity found in liver. Estimated body burdens at 72 h following intragastric dosing averaged 0.013 (no cannula) and 0.011 (bile cannulated) of dose, values which were less than 0.10 of those found in intact (no bile duct cannula) animals given i.v. doses.

Castrates fed diets containing 3 ppm [^{14}C]FB_1 (1.2 μCi/mg) for 12 days, followed by 2 ppm for an additional 12 days and then by clean feed for 9 days were euthanized, starting on day 3, to follow the time-course of deposition of radioactivity in tissues (Prelusky et al., 1996b). As in previous studies, the liver and kidneys contained the highest specific activities at all time periods and radioactivity appeared in bile. Liver- and kidney-specific activity rose continuously and their respective tissue burdens were calculated to be approximately 160 and 65 ng/g at the conclusion of the 24-day exposure period. Although specific activity of the tissues declined after returning the animals to control feed, small amounts of radioactivity remained in the liver and kidney at the end of the study. Overall, the results of studies carried out by Prelusky et al. (1994, 1996a,b) showed that the absorption of FB_1 from feed is low, that the mycotoxin remains in the tissues for an extended period of time, that the absorbed FB_1 preferentially accumulates in liver and kidneys, and that enterohepatic recirculation contributes to the long biological half-life of the mycotoxin.

3.3. Ruminants

Fumonisin is minimally absorbed by ruminants, which may partly explain their tolerance to ingestion of this toxin. In steers given FB_1 and FB_2, more than 0.80 of the total ingested mycotoxin was unmetabolized and excreted in the faeces, with trace amounts found in the urine (Smith and Thakur, 1996). In studies examining rumenal metabolism, there was minimal degradation of FB_1 (less than 100 ppm from culture material) by microbes present in rumenal fluid over a 72 h period and no effect on microbial efficiency (Gurung et al., 1999).

Prelusky et al. (1995) reported on the bioavailability of FB_1 in lactating dairy cows given i.v. doses of 0.05 or 0.2 mg/kg body weight or oral doses of 1 or 5 mg/kg body weight Clearance of FB_1 from the i.v.-dosed animals was bi-exponential with a $t_{1/2\,\alpha}$ of 1.7 min and a $t_{1/2\,\beta}$ of 15.1 min (low dose) to 18.7 min (high dose). FB_1 was not detected in the plasma after 2 h and the low volume of distribution (0.251–0.278) suggested that the FB_1 was poorly taken up by the tissues. FB_1 was not detected in plasma of orally dosed cows. The authors offered several possible explanations for the latter observation: absorption was negligible; the rapid clearance from plasma of the low amounts of absorbed mycotoxin kept serum levels below the limit of detection; or the first-pass through the liver reduced blood FB_1 concentrations to undetectable levels. In the one study using goats, only 0.50 of ingested fumonisin was excreted unmetabolized in the faeces over a 112-day dosing period (Gurung et al., 1998).

3.4. Poultry

Following i.v. administration of FB_1 to laying hens (2.0 mg/kg body weight corresponding to 0.64 μCi/kg body weight), clearance of the radiolabel from plasma was bi-exponential: $t_{1/2\,\alpha} = 2.5$ min and $t_{1/2\,\beta} = 49$ min (Vudathula et al., 1994). The radioactivity was not distributed to the tissues and, accordingly, only trace amounts were detected in liver and kidneys and none in other tissues after 24 h. After oral dosing (2.0 mg/kg body weight corresponding to 1.28 μCi/kg body weight), absorption of $[^{14}C]FB_1$ was about 0.02 of the dose and, similarly to i.v. injection, the radiolabel was eliminated very rapidly. Only a few tissues, including the gastrointestinal tract (crop, small intestine and cecum), liver and kidney, had detectable amounts ($\leq$0.01 of the oral dose) of radioactivity remaining after 24 h.

3.5. Fumonisin residues in meat, milk, and eggs

From the data summarized above and the review of Prelusky et al. (1996b), little FB_1 accumulates in edible tissues, except for liver and kidney, of pigs, cattle and poultry. However, the potential for fumonisin contamination in animal food products such as milk and eggs is of concern due to their widespread consumption and, especially for milk, the exposure potential in children. Potential exposure to fumonisins from milk is also of agricultural concern because of possible economic loss to farmers by reducing growth and otherwise adversely affecting calves, piglets or other young animals.

Neither FB_1 nor hydrolyzed FB_1 were detected in the milk (limits of detection [LOD] for FB_1 and HFB_1 were 3 and 20 ng/ml, respectively) of dairy cows dosed orally (up to 5 mg/kg body weight) or i.v. (up to 0.2 mg/kg body weight) with $[^{14}C]FB_1$ (Scott et al., 1994). β-Sulphatase/glucuronidase treatment of the milk failed to liberate detectable FB_1. The authors calculated that the 5 mg/kg body weight oral dose was about equal to that incurred after ingesting feed containing 125 ppm FB_1 and the i.v. dose of 0.2 mg/kg body weight FB_1 corresponded to a dietary intake of feed contaminated with about 500 ppm of the mycotoxin, assuming that the bioavailability of FB_1 from feed was about 0.01 (Prelusky et al., 1996b). Fumonisins were also not detected (LOD = 5 ng/ml) in the milk of two dairy cows fed diets containing about 75 ppm fumonisins (daily intake of FB_1 was about 3 mg/kg body weight) for 14 days (Richard et al., 1996). Using the isolated perfused bovine udder, Hammer et al. (1996) found ≤0.0011 of administered FB_1, given i.v., in the milk and Spotti et al. (2001) also found minimal FB_1 carry over into milk. Furthermore, FB_1 was not found in 154 of 155 milk samples surveyed in Wisconsin, USA and only low levels of FB_1 were detected in the positive sample (Maragos and Richard, 1994). Overall, the results of these studies indicate that carryover of FB_1 into milk does not pose a threat to consumer health.

Similarly, FB_1 was not found in the milk (LOD = 30 ng/ml) of sows that were fed diets supplemented with FB_1 (100 ppm) for 14 days (Becker et al., 1995). Zomborszky-Kovacs et al. (2000) did detect low levels (≤28 μg/l) of FB_1 in the milk of sows fed 300 mg fumonisins (provided from fungal culture material) daily for 7 days prior to and following parturition. The milk of mink fed fumonisins contained low levels of these mycotoxins (approximately 0.007 of the dietary fumonisin concentration); however, the nursing kits were not adversely affected (Powell et al., 1996). Together, these observations suggest that exposure to fumonisins through milk does not pose a production or health concern to suckling pigs or mink.

Vudathula et al. (1994) did not find any evidence for the carryover of fumonisin into eggs during experiments in which laying hens were given single doses of 2.0 mg/kg $[^{14}C]FB_1$ by the oral or i.v. routes.

4. Disruption of sphingolipid metabolism and mechanism of action

4.1. Fumonisins disrupt sphingolipid metabolism

The mechanism of action of fumonisins does not depend upon metabolic activation as there is no evidence that they or their hydrolyzed forms are metabolized by Phase I or II

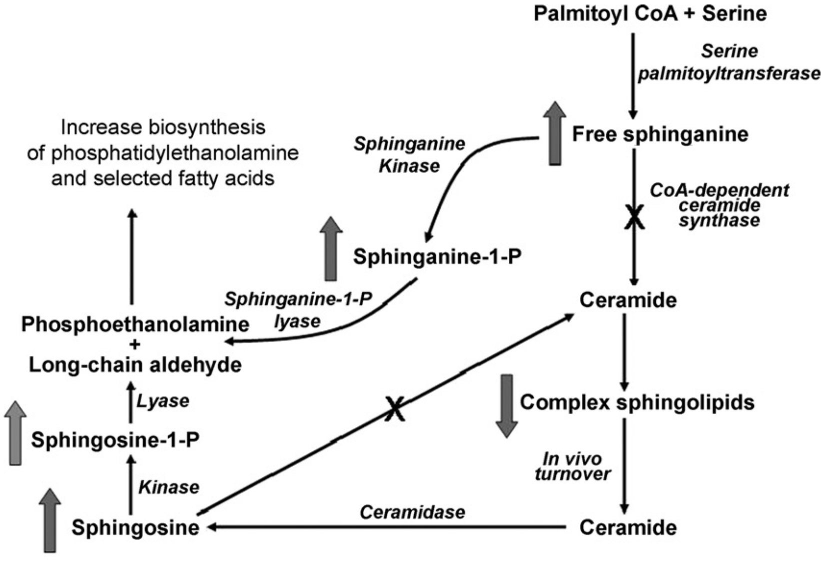

Fig. 2. Summary schematic of sphingolipid metabolism showing the inhibition of ceramide synthase (×) by fumonisins. Inhibition blocks the formation of ceramide from sphinganine and fatty acyl-CoA (not shown in figure) via *de novo* synthesis or from sphingosine produced by the ceramidase-mediated breakdown of ceramide. The consequences of ceramide synthase inhibition include increased tissue and serum concentrations (up arrows) of sphinganine (to a lesser extent), sphingosine, and their 1-phosphate metabolites as well as decreases (down arrow) in complex sphingolipids downstream of ceramide (Merrill et al., 2001; Riley and Voss, 2006).

enzymes (Bolger et al., 2001). Fumonisins having a (unsubstituted) primary amino group at C2 competitively inhibit ceramide synthase and, as a result, disrupt the *de novo* biosynthesis of ceramide and sphingolipid metabolism (Fig. 2) (Merrill et al., 2001; Riley et al., 2001; Riley and Voss, 2006).

An immediate consequence of ceramide synthase inhibition is accumulation of the enzyme's sphingoid base substrates sphinganine (Sa) and, to a lesser degree, sphingosine (So) in tissues, serum, and urine. Accumulation of sphingoid bases and the accompanying increase in the Sa:So ratio in tissues following fumonisin exposure have been demonstrated in a variety of mammalian, avian, and piscine species (reviewed Bolger et al., 2001; Haschek et al., 2001) and have proven to be useful biomarkers of exposure in experimental situations (Merrill et al., 2001; Riley et al., 2001). The use of Sa and Sa:So as exposure biomarkers in human populations has been limited and their usefulness for epidemiological studies is not established (van der Westhuizen et al., 1999; Abnet et al., 2001; Sewram et al., 2003; Solfrizzo et al., 2004; Missmer et al., 2006). The use of increased serum, urine or tissue Sa concentrations for confirming fumonisin exposure in farm animals in the field can be useful although it must be kept in mind that fumonisin-induced changes in sphingoid base profiles are reversible (Wang et al., 1992; Voss et al., 1998; Enongene et al., 2002). In the case of ponies (Wang et al., 1992), serum sphingoid base concentrations and alanine and aspartate transaminase activities rose and fell together as fumonisin-contaminated feed was ingested or avoided by the animals.

The 1-phosphate metabolite of Sa accumulates in serum and Sa 1-phosphate, and to a lessor extent So 1-phosphate, accumulate in tissues following fumonisin exposure (Piva et al., 2005; Haschek et al., 2006; Riley and Voss, 2006; Tardieu et al., 2006; Tran et al., 2006). The increases in Sa 1-phosphate and So 1-phosphate in kidney of rats were, like those of Sa and So, dose- and time-dependent and, while they lagged behind Sa and So, the increases in the 1-phosphate metabolites still occurred prior to or concurrent with the appearance of kidney lesions (Riley and Voss, 2006). In contrast, Sa and So 1-phosphates did not accumulate in liver. The reason for this is not known but might be related to differences between the two organs in one or more of the following: rate of conversion of Sa and So to their 1-phosphates (kinase activity), metabolism of the sphingoid base 1-phosphates to aldehydes and phosphoethanolamine (lyase activity), dephosphorylation of the Sa or So 1-phosphates (phosphatase activity), or the uptake and excretion of the 1-phosphate metabolites (Riley and Voss, 2006).

4.2. *Sphingolipids as mediators of toxicity*

A correlation between Sa accumulation and the onset of apoptosis (the earliest microscopic evidence of tissue injury) and mitosis in response to fumonisin exposure has repeatedly been shown in the liver and kidney of rats (Riley et al., 1994; Howard et al., 2001a; Riley and Voss, 2006), mice (Tsunoda et al., 1998; Sharma et al., 2002) and rabbits (Gumprecht et al., 1995), in the liver of pigs (Gumprecht et al., 1998), and of changes in serum indicators of liver damage in ponies (Wang et al., 1992; Riley et al., 1997). Sa and So exert proapoptotic, cytotoxic, and growth inhibitory effects and it is therefore attractive to propose that they mediate fumonisin toxicity (Merrill et al., 2001). However, other consequences of ceramide synthase inhibition are reduced ceramide and increased So 1-phosphate concentrations, both of which have been shown to inhibit apoptosis and promote mitosis and regeneration (Merrill et al., 2001; Spiegel and Milstien, 2002).

The possibility that sphingoid base 1-phosphates are mechanistically involved in some of fumonisin's toxic effects is also intriguing and gaining attention. The kidney of male Sprague–Dawley (Riley et al., 1994; Voss et al., 2001) and Fischer 344 (Howard et al., 2001a,b) rats are very sensitive to fumonisin-induced apoptosis and, in this regard, it is of interest that i.v. administration of So 1-phosphate (Sa 1-phosphate was not tested) to rats reduced renal and mesenteric blood flow (Bischoff et al., 2001). Pretreatment with pertussis toxin abolished the vasoconstrictive effect, suggesting that a G protein-coupled So 1-phosphate receptor (S1PR, a class of cell surface receptors formerly known as endothelial differentiation gene or Edg receptors) was involved. G protein-coupled S1PR are now well recognized mediators of a broad range of extracellular signaling pathways affecting cell proliferation and survival, cell migration, cell to cell adhesion and immunity (Pyne and Pyne, 2000; reviewed by Hla, 2004). There is evidence that fumonisins variably modulate immunity and host resistance (Tryphonas et al., 1997; Johnson and Sharma, 2001; Dresden-Osborne et al., 2002; Deshmukh et al., 2005; Taranu et al., 2005) and inhibit cell to cell or cell to matrix adhesion (Pelagalli et al., 1999; Gon et al., 2005).

Complex sphingolipids (CSL) are downstream metabolic products of ceramide. CSL concentrations decrease in serum or tissues of fumonisin-exposed animals (Wang et al., 1992; Riley et al., 1994) and it is feasible that reduced CSL *per se* or disruption of CSLdependent processes mediate some of fumonisins' effects. For example, Stevens and Tang (1997) found that FB_1 disrupted 5-methyltetrahydrofolate uptake and binding capacity in Caco-2 cells through a mechanism mediated by the depletion of sphingolipids, presumably those associated with membrane lipid rafts involved in folate transport.

5. Toxicity in laboratory animals

5.1. Toxicity, target organs and pathology

The toxicological and pathological effects of fumonisins have been extensively studied in laboratory animals. Comprehensive reviews of the subject are available (Bucci et al., 1998; Bolger et al., 2001; Dragan et al., 2001; Hard et al., 2001; Voss et al., 2001) and therefore only the main points are summarized here. The liver and kidney are the major target organs but species-, strain-, and sex-dependent differences in dose–response occur. For example, the no observed effect and lowest observed effect levels for kidney are lower than those for liver in Sprague–Dawley (Riley et al., 1994) and Fischer 344 (Voss et al., 1995; Howard et al., 2001a,b) rats and males are more sensitive than females in regard to nephrotoxicity. This is not the case however for the BD IX rat, in which the liver is the only major target organ (Gelderblom et al., 1988, 1991). Rabbits are very sensitive to the renal effects of FB_1 (Gumprecht et al., 1995; Bucci et al., 1998) while mice are less sensitive to nephrotoxicity than Sprague–Dawley or Fischer 344 rats (Sharma et al., 1997; Bucci et al., 1998; Howard et al., 2001b).

In both liver and kidney, apoptosis alone or together with increased mitosis is an early microscopic indication of tissue injury (Lim et al., 1996; reviewed by Bolger et al., 2001; Voss et al., 2001). Cytomegaly, anisocytosis, anisokaryosis, cytoplasmic vacuolation (hepatocellular) and necrosis become evident in both tissues with increasing dose. Biliary epithelial or oval cell proliferation, foci of cellular alteration, and fibrosis have also been observed in more advanced liver lesions. Kidney lesions are at first confined to the proximal tubules of the outer medulla (in some reports designated as the corticomedullary junction) (Voss et al., 1995; Lim et al., 1996; Bucci et al., 1998; Hard et al., 2001) and characterized by detachment and sloughing of the apoptotic epithelial cells (small, round, with pyknotic nuclei) into the lumen. This is accompanied by an increase in the number of mitoses in the tubular epithelium and, as the severity of injury and regeneration increase, the epithelium displays cytoplasmic basophilia and is more cuboidal. Foci of tubular hyperplasia may also be present. Severely damaged kidneys exhibit progressively more apoptosis and sloughing, tubular atrophy, focal tubular hyperplasia, interstitial fibrosis, inflammation and, in the most severe cases, overt tubular necrosis.

5.2. Carcinogenicity

Maize naturally contaminated with *Fusarium* sp. or experimentally contaminated with a strain of *F. verticillioides* associated with a field outbreak of ELEM caused neoplastic and preneoplastic lesions in rats (Wilson et al., 1985). Likewise, chronic dietary exposure to FB_1 ($\geq$50 ppm) is carcinogenic to rodents: hepatocarcinogenic in male BD IX rats (Gelderblom et al., 1991) and female B6C3F$_1$ mice (Howard et al., 2001a) and nephrocarcinogenic in male F344 rats (Howard et al., 2001a). It is of interest that some of the kidney tumors were highly anaplastic and sarcomatous in appearance, an unusual manifestation in chemically induced renal tumors (Hard et al., 2001). The aggressiveness of these tumors was confirmed by their local invasiveness and the presence of metastases in remote locations. The weight of evidence indicates that the mechanism of carcinogenesis is epigenetic and related to compensatory cell proliferation that accompanies apoptosis (Bolger et al., 2001; Dragan et al., 2001).

5.3. *Reproductive and developmental effects*

Reduced reproductive performance in livestock can have a significant economic impact (Council for Agricultural Science and Technology, 2003). However, most studies on the reproductive effects of fumonisins have used laboratory animals. *F. verticillioides* and FB$_1$ were variably fetotoxic at maternally toxic doses (Reddy et al., 1996; Voss et al., 1996; Collins et al., 1998; LaBorde et al., 1997). Fetotoxicity in the absence of maternal toxicity has also been reported (Lebepe-Mazur et al., 1995; Penner et al., 1998), however, maternal toxicity might have been underestimated in these studies because tissue or serum sphingolipid analyses were not included in the experimental protocols. In rats, studies on fetal tissue Sa:So ratios as well as the biodistribution of [^{14}C]FB$_1$ after its i.v. administration to pregnant dams on gestation day (GD) 15 did not provide evidence that FB$_1$ crossed the placenta (Reddy et al., 1996; Voss et al., 1996; LaBorde et al., 1997). However, subsequent studies showed that FB$_1$ crossed the placenta of LM/Bc mice that were given FB$_1$ i.v. on GD10.5 (Gelineau-van Waes et al., 2005) or fed diets containing 150 ppm FB$_1$ for more than 5 weeks (Voss et al., 2006b). Possible explanations for the different results of these studies include: species and strain-related differences in placental physiology, differences in the timing of dose administration (stage of placental development at exposure), or the time elapsed between dosing and tissue sampling (reversibility of sphingolipid effects in the fetal tissues).

Unlike in previous studies, in this inbred LM/Bc mouse strain, FB$_1$ was also teratogenic, inducing neural tube defects when given intraperitoneally (i.p.) to the pregnant dams (Gelineau-van Waes et al., 2005). As predicted from the results of Stevens and Tang (1997), FB$_1$ reduced folate uptake (folate deficiency is a risk factor for neural tube defects) by the embryos and the amount of folate binding protein (folbp1; a high affinity transporter for folate found in the placenta) in the yolk sac membrane. Interestingly, folbp1 is a glycosylphosphatidylinositol (GPI)-anchored protein associated with sphingolipid-rich membrane domains in cell membranes known as lipid rafts (Stevens and Tang, 1997) and it co-localized with the complex sphingolipid GM$_1$ in the yolk sac membrane of the LM/Bc mice. Induction of neural tube defects by FB$_1$ was significantly reduced when the pregnant LM/Bc females were also given folate or GM$_1$, with GM$_1$ being the more effective of the two co-treatments (Gelineau-van Waes et al., 2005). While less sensitive than the LM/Bc strain, CD1 mice exposed to FB$_1$ also developed neural tube defects (Voss et al., 2006b) when dosed by the i.p. injection protocol of Gelineau-van Waes et al. (2005). The mechanism of FB$_1$-induced neural tube defects in mice remains to be elucidated and might include both direct (fetal exposure) as well as indirect (decreased folate resulting from complex sphingolipid depletion in the dams) mechanisms.

6. Fumonisins and domestic animals

Fumonisins induce spontaneous disease in horses and pigs, with horses being the more susceptible species. These diseases, equine leukoencephalomalacia (ELEM) and porcine pulmonary edema (PPE), refer to critical species-specific target organs, the brain in horses and the lung in pigs. Similar to laboratory species, the liver, and occasionally the kidney, are also target organs. Cardiotoxicity, the most recently recognized type of toxicity, has been reported in pigs and horses (Smith et al., 1996, 2002). In pigs, cardiotoxicity appears to be the cause of pulmonary edema, which is usually lethal (Smith et al., 1999). Since pigs are an excellent animal model for human diseases, the manifestations of fumonisin toxicoses in pigs need to be carefully considered in risk assessment.

The level of fumonisin contamination required to induce ELEM, which is unique to *Equidae*, is quite low, therefore fumonisin toxicosis in horses occurs periodically throughout the USA. More highly contaminated feed is required to induce PPE in pigs and few, if any, outbreaks have been documented in the USA since the highly contaminated 1989 maize crop. However in 2006, an outbreak of PPE was documented in Illinois based on elevated serum sphingolipids (Hsiao et al., 2007). Cattle and poultry are much more resistant to fumonisins than horses or pigs.

Experimental data are readily available regarding the effects of fumonisins in horses, cattle and poultry, but are rather limited for fish and mink. Most of the experiments have been performed using *F. verticillioides* culture material although purified FB_1 has been used for some studies. Experimental data are nonexistent for cats and dogs. Information regarding the toxicity of fumonisins in these species would be useful given the occasional occurrence of mycotoxicoses caused by contaminated pet food.

In addition to the life-threatening effects of fumonisins discussed above, effects on the immune system have also been reported. Adverse effects on immune function can increase susceptibility to opportunistic microorganisms or result in more severe infections, including those related to food safety and zoonotic diseases. In addition, immune suppression can interfere with vaccination responses and can predispose to cancer induction. The effects of long term, low level exposures on the immune system are especially important.

As in laboratory animals, exposure to fumonisins in farm animals causes sphingolipid alterations in most tissues as well as in serum and, to a lesser extent, urine. These alterations are characterized by a dose- and time-dependent elevation in the concentration of free Sa, with a corresponding increase in the Sa:So ratio. Because these alterations occur very rapidly and at low levels of exposure, they can be used as biomarkers experimentally and, with some caveats, diagnostically. More recently, significant increases in Sa 1-phosphate have been documented in serum from pigs and horses and in duck liver following exposure to fumonisins (Piva et al., 2005; Haschek et al., 2006; Tardieu et al., 2006).

Fumonisin toxicosis can be diagnosed based on clinical signs, microscopic changes, and the presence of fumonisins at toxic concentrations in the feed. While sphingolipid alterations in serum, urine and tissues, can confirm exposure to fumonisins, they are transient. In addition, sphingolipid analysis is not yet routinely available for diagnostic purposes. Prevention is the key to avoiding fumonisin toxicoses since treatment is not available. The USFDA and European Union have issued guidance levels for total fumonisins in animal feed, which are given in Tables 1 and 2, respectively.

6.1. Equidae and equine leukoencephalomalacia (ELEM)

Horses are the most sensitive species to fumonisin toxicity with naturally occurring disease occurring worldwide. The target organs in the horse are heart, central nervous system and liver. The disease syndrome was named leukoencephalomalacia due to the type (malacia = softening [due to necrosis]) and distribution (leuko = white matter) of the most prominent lesion in the brain. Equids are the only species in which fumonisins induce this lesion. Several reviews of ELEM are available (Haliburton and Buck, 1986; Haschek and Halibuton, 1986; Diaz and Boermans, 1994). Onset of disease may occur as early as 7 days after a change in diet, but usually after 14–21 days; occasionally onset may be delayed 90 days or more. Outbreaks that affect several horses on the same farm are common. For additional information on outbreaks see Morgavi and Riley (2007). In 1901 through 1902, over 2000 horses died in the USA as a result of ELEM and in 1934 through 1935 over 5000 horses died in the state of Illinois alone. Large numbers of outbreaks were reported in the USA during the 1980s, especially following the heavy contamination of the 1989 maize crop (Brownie and Cullen, 1987; Ross et al., 1991). Additional outbreaks of ELEM were reported in the mid-1990s from the USA and Hungary (Bela and Endre, 1996). Outbreaks continue to occur each year in the USA. In a given outbreak, the overall morbidity is generally low, less than 0.25; but mortality usually approaches 1.00 in affected animals. The rare surviving animals will usually have permanent neurological disease. ELEM also occurs in donkeys.

Two syndromes have been described in horses with naturally occurring disease due to *F. verticillioides* or *F. proliferatum* infection of maize, the neurotoxic (which is termed ELEM) and hepatotoxic forms. These forms may appear independently or concurrently. In the field, high-dose exposure is thought to increase the likelihood of the hepatotoxic form, with the more frequently encountered lower doses favoring the neurotoxic form, ELEM. The clinical course of ELEM is generally short with an acute onset of signs followed by death within hours or days. Decreased feed intake, depression, ataxia, blindness, and hysteria are reported. Anorexia occurs due to glossopharyngeal paralysis, and paralysis of the lips and tongue, with loss of ability to grasp and chew food. Incoordination, circling, ataxia, head pressing, marked stupor, and hyperesthesia are common, as are hyperexcitability, profuse sweating, mania, and convulsions. Acutely affected animals often progress through the manic and depressive stages of the syndrome within 4–12 h of onset and become recumbent and moribund. Death may also occur without clinical signs being observed.

In classical ELEM, there is liquefactive necrosis of the white matter, primarily in the cerebrum, which is often evident grossly as cavitation or discoloration. However these lesions are not observed in all cases. Histologically, necrosis with influx of macrophages (gitter cells), edema, and hemorrhage are primary findings.

The hepatotoxic syndrome occurs much less frequently than the neurotoxic form and, based on the authors' experience, is not currently being identified. This syndrome usually takes 5–10 days from time of onset of clinical signs to death. Icterus is usually prominent, sometimes with edema of the head and submandibular space, as well as oral petechia. Elevated serum bilirubin concentration and liver enzyme activities are typically present. Neurologic signs may be present terminally. The liver is often small and firm, with an increased lobular pattern. Centrilobular necrosis and moderate to marked periportal fibrosis can be observed histologically.

Neurotoxicity and hepatotoxicity have been reproduced experimentally in horses, ponies and donkeys by feeding naturally contaminated feed, fumonisin containing culture material and purified FB_1 (Brownie and Cullen, 1987; Wilson and Maronpot, 1971; Marasas et al., 1988; Kellerman et al., 1990; Ross et al., 1992; Foreman et al., 2004). Unlike past observations of spontaneous disease, neurologic and hepatic disease generally occurred concurrently. However, not all horses developed disease and not all horses with neurologic disease had classical leukoencephalomalacia. Important factors in the development and expression of ELEM following oral exposure included length of exposure, level of dietary contamination, individual susceptibility and previous exposure to fumonisins (Ross et al., 1993). Intravenous administration of FB_1 induced clinical signs and a time-course for neurologic disease similar to that in naturally occurring disease (Foreman et al., 2004).

Cardiotoxicity was documented following administration of 1 mg purified FB_1/kg i.v. daily for 4–7 days (Smith et al., 2002). Cardiovascular abnormalities were present in horses with neurologic disease and were similar to those described for pigs below, including decreased cardiac contractility, heart rate, arterial pulse pressure and increased systemic vascular resistance (Smith et al., 2002).

Serum parameters indicative of liver damage as well as cholesterol were increased in most studies. Similarly to other species, Sa and So levels were elevated in serum and tissues such as heart, liver, and kidney but minimally, if at all, in brain (Wang et al., 1992; Goel et al., 1996). These findings suggest that neurologic injury is not a direct effect of sphingolipid alterations in the brain.

6.2. Pigs and porcine pulmonary edema (PPE)

Reviews of fumonisin toxicosis in pigs are available (Diaz and Boermans, 1994; Haschek et al., 2001). Outbreaks of a fatal disease in pigs fed *F. verticillioides*-contaminated maize screenings from the 1989 maize crop in mid-western and south-eastern USA led to the identification of FB_1 as the causative agent of PPE (Osweiler et al., 1992). Thousands of pigs died in these outbreaks. In Hungary, outbreaks of this disease have been observed since the 1950s (Fazekas et al., 1998). A decline in feed consumption is usually the first sign following fumonisin exposure. Within 4–7 days of initial feeding of highly contaminated feed, pigs show respiratory distress and cyanosis that is rapidly followed by death due to acute pulmonary edema and hydrothorax (Haschek et al., 1992). Typically, deaths cease within 48 h of withdrawal of contaminated food.

Porcine pulmonary edema has been reproduced experimentally in pigs by feeding naturally contaminated feed, fumonisin containing culture material and purified FB_1 (Haschek et al., 1992; Colvin et al., 1993; Smith et al., 1996, 2000; Gumprecht et al., 1998). As in the naturally occurring situation, exposure to fumonisins for 4–7 days is required before respiratory distress and, sometimes, cyanosis due to pulmonary edema is clinically evident. The pulmonary edema is a species-specific effect and has not been reported as a major finding in any other species. Death occurs within hours of respiratory distress or without clinical signs. Severe pulmonary edema and hydrothorax are present. Edema appears to originate in the interstitium with perivascular edema and markedly dilated lymphatics as a prominent feature early in the disease. Non-lethal pulmonary edema has also been reported following longer term, lower dose exposures (Zomborszky-Kovacs et al., 2000).

Acute liver injury is similar to that found in other species and is characterized by scattered hepatocellular apoptosis, necrosis and mitosis (Gumprecht et al., 1998; Haschek et al., 2001). Pancreatic necrosis has been reported in some studies. Alterations in clinical pathology reflect hepatic injury, and serum cholesterol concentration is elevated. At lower doses, hepatic injury is the dominant feature and slowly progressive liver disease may occur. Subacute hepatic injury is characterized by hepatocellular cytomegaly, disorganization of hepatic cords, and early perilobular fibrosis while chronic injury is characterized by icterus with severe hepatic fibrosis and nodular hyperplasia (Casteel et al., 1993, 1994). Additional findings reported from these chronic studies include esophageal plaques and right ventricular hypertrophy due to pulmonary hypertension (Casteel et al., 1993, 1994).

Experimentally, progressive and marked elevations in Sa and So are found in serum and major organs such as kidney, liver, lung, and heart indicating a major disruption in sphingolipid metabolism (Riley et al., 1993; Gumprecht et al., 1998; Smith et al., 1999). In the recent field outbreak of porcine pulmonary edema investigated by our laboratory, average serum Sa concentration was 1.67 μM, So was 5.30 μM and Sa:So was 3.22 (Hsiao et al., 2007). Respective experimental control values were $\leq$ 0.06 μM, $\leq$ 0.07 μM and $\leq$ 0.18.

FB_1 decreases cardiac contractility, mean systemic arterial pressure, heart rate and cardiac output, and increases mean pulmonary artery pressure and pulmonary artery wedge pressure (Constable et al., 2000, 2003). Therefore, fumonisin-induced pulmonary edema appears to result from acute left-sided heart failure (Smith et al., 1999) and the findings are compatible with the inhibition of L-type calcium channels due to increased So and/or Sa concentrations in the heart. More recently, So 1-phosphate has also been implicated in the pathogenesis of the vascular alterations *in vitro* (Hsiao et al., 2005) and was significantly elevated in the serum of pigs fed diets containing 30 μg fumonisin B_1/g (Piva et al., 2005).

Because multiple mycotoxins are frequently found in feed, the interactions of fumonisins with aflatoxin B_1 and moniliformin have been examined (Harvey et al., 2002; Dilkin et al., 2003). Study results generally have indicated an additive rather than synergistic interaction.

Effects on both specific and non-specific immunity of pigs have been reported (Casteel et al., 1993; Harvey et al., 1995, 1996). FB_1 decreased phagocytosis and inhibited sphingolipid biosynthesis in pigs pulmonary macrophages, and decreased clearance of particulates and bacteria from the pulmonary circulation (Smith et al., 1996; Haschek et al., 2001). Intratracheal instillation with non-toxin producing type A *Pasteurella multocida* resulted in interstitial pneumonia in pigs previously gavaged with 0.5 mg FB_1 (from culture material)/kg day for 7 days but not in those without FB_1 treatment (Halloy et al., 2005). Pigs similarly treated with fumonisins had increased intestinal colonization by pathogenic *E. coli* (Oswald et al., 2003).

6.3. Ruminants

Maize screenings are part of a basal diet for ruminants such as cattle and sheep in the USA, making fumonisin toxicity and excretion in the milk a concern in ruminants. However, naturally occurring toxicosis has not been reported and little to no fumonisin is excreted in the milk (see Section 3.5). Cattle and other ruminants have been reported to go off feed that is contaminated with fumonisins and will consume clean feed when offered.

Experimentally, fumonisin is hepatoxic and nephrotoxic to calves whether given orally or i.v. In a high dose, short term study, Holstein milk-fed calves given 1 mg FB_1/kg body weight i.v. for 7 days had hepatic and renal damage after 2–4 days of treatment as determined by serum and urine biochemistry (Mathur et al., 2001a). The calves were lethargic and had decreased appetite. Mild hepatocellular apoptosis and severe renal tubular necrosis were present at 7 days. Unlike pigs and horses, cardiovascular function was unaffected (Mathur et al., 2001b). Increases in Sa and So concentrations were found in liver, kidney, lung, heart and skeletal muscle of these calves (Mathur et al., 2001a). Sa but not So concentrations were increased in serum and brain (Mathur et al., 2001a,b). In a similar study, changes in plasma Sa and So concentrations were not present in calves given 0.05 mg FB_1/kg i.v.; however, plasma Sa concentrations increased at 1.0 mg/kg i.v. (Prelusky et al., 1995). In cows given one oral dose (5.0 mg/kg body weight) of FB_1, plasma Sa or So concentrations were not altered (Prelusky et al., 1995).

In lower dose, longer term studies, beef calves given feed containing a total fumonisin concentration of 148 ppm (FB_1, FB_2 and FB_3) for 31 days had serum biochemical and histologic evidence of hepatic damage, as well as impairment of lymphocyte blastogenesis but not other immune parameters (Osweiler et al., 1993). Hepatic injury was induced in three Holstein calves fed maize containing a total fumonisin concentration of 440 ppm (328 ppm FB_1, 89 ppm FB_2, and 23 ppm FB_3) from culture material daily up to 0.0107 of body weight (FB_1 consumption was up to 3.54 mg/kg body weight); serum aspartate transaminase and γ-glutamyltranspeptidase activities increased starting at 4 weeks of exposure and mild morphologic alterations were present in the liver at the end of the 9-month study (Baker and Rottinghaus, 1999).

Oral exposure to fumonisins from *F. verticilloides* culture material in lambs and goat kids presents with similar biochemical indices and histologic findings to calves, indicative of renal and mild hepatic toxicity (Edrington et al., 1995; Gurung et al., 1998). Lambs given 45.5 mg fumonisins (FB_1, FB_2, and FB_3) daily died within 7 days with severe renal injury (Edrington et al., 1995). Clinical signs of toxicity were not observed when goats were given 95 mg FB_1/kg of diet for 112 days (Gurung et al., 1998). Similarly to calves, goats had increased Sa and So concentrations in liver, kidney and heart (Gurung et al., 1998).

6.4. *Poultry*

Fumonisins are of concern in poultry because maize usually comprises approximately 0.50 of poultry diets in the United States (reviewed by Diaz and Boermans, 1994). However, poultry are relatively resistant to fumonisin toxicity. Data from studies where *F. verticilloides* culture material comprised greater than 100 g/kg diet in order to achieve toxic levels of fumonisins must be interpreted with caution since other toxins present in the culture material may have contributed to the observed toxicity (Weibking et al., 1993a). One-day-old chicks fed diets containing 100–400 mg FB_1/kg from culture material for 21 days had decreased (dose-dependent) weight gain, increased liver weights (dose-dependent), hepatic necrosis (≥200 ppm fumonisin), biliary hyperplasia (≥300 ppm), and thymic cortical atrophy (≥100 ppm) (Ledoux et al., 1992). Similar results were found in a second study, in which Sa levels and Sa:So ratios increased in serum at all doses (≥75 ppm) (Weibking et al., 1993a). Similarly, purified FB_1 incorporated into the diet at 20–80 mg/kg increased Sa in the liver at all doses and in serum at 80 mg/kg; at this dose hepatic enzymes were elevated but no other effects were observed (Henry et al., 2000).

In turkey poults fed fumonisin containing culture material, similar changes to those in chicks were found, although turkeys may be more susceptible to long term effects of fumonisins (Weibking et al., 1993b; Broomhead et al., 2002). Mallard ducks force-fed naturally contaminated maize containing 20 mg FB_1/kg for 12 days had 8% mortality and decreased feed conversion ratio, while increased Sa in liver and plasma was observed at ≥10 mg/kg (Tardieu et al., 2004). In other duck studies, hepatic injury was observed at 5 mg FB_1 (from culture material)/kg body weight following oral administration for 12 days (Bailly et al., 2001) and serum Sa:So ratios were increased at levels as low as 2 mg FB_1/kg feed (Tran et al., 2006).

A potential effect on the immune system of poultry was identified in *in vitro* studies. FB_1 was cytotoxic to turkey lymphocytes and decreased the phagocytic potential of chicken peritoneal macrophages (Qureshi and Hagler, 1992; Dombrink-Kurtzman et al., 1994). More recently, FB_1 (≤50 μg/ml) decreased cell viability and mitogenic response in splenic cells but not thymocytes or blood lymphocytes (Keck and Bodine, 2006). Continuous presence of FB_1 (150 mg/kg, from culture material) in the diet of quail chicks appeared to increase the susceptibility to and severity of *Salmonella gallinarum* infection as manifested by increased severity of diarrhea and increased mortality (Deshmukh et al., 2005)

6.5. Mink

Cereal grains are an important component of ranch mink diets. Adult female mink (*Mustela vison*) fed diets containing 118 ppm total fumonisins from culture material for 87 days did not have clinical evidence of disease, apart from lethargy (Restum et al., 1995). Although clinicopathologic changes in serum indicated hepatic, renal and pancreatic injury, morphologic alterations were not found by histological examination. Concentrations of free Sa and the Sa:So ratio were increased in liver and kidney. Another study was conducted to evaluate the effects of fumonisin on reproductive performance of female mink. Diets containing 115 or 254 ppm total fumonisins were fed through breeding, gestation and lactation without effect on breeding performance (Powell et al., 1996). However, only 0.58 of the high-dose group mink whelped and there was a dose-dependent decrease in kit body weights at birth. By 7 days, at these doses, Sa and So concentrations were increased in urine, but not hair, suggesting that urinary Sa:So ratios could be used as a biomarker of exposure (Morgan et al., 1997). Taken together, the data suggest that mink are not very susceptible to fumonisin toxicity.

6.6. Fish

Maize is a major component of fish feed and catfish food typically contains 300–350 g maize/kg in the USA. Because of the potential health effects in farm-raised fish, the effects of fumonisins have been examined in channel catfish (*Ictalurus punctatus*) and carp (*Cyprinus carpio* L.). In addition, trout have been used as a model to examine the carcinogenic potential of fumonisins. Adult channel catfish tolerated feed containing up to 313 mg FB_1 (from culture material)/kg for periods up to 5 weeks without histological evidence of toxicity (Brown et al., 1994). In a separate series of feeding studies, diets containing $\geq$20 mg FB_1 (from culture material)/kg were toxic to adult channel catfish when fed for 10–14 weeks; decreased weight gain, altered hematological parameters, morphologic hepatic alterations, and decreased resistance to bacterial challenge with *Edwardsiella ictaluri* were found. Significant mortality occurred at 320 and 720 mg FB_1/kg (Lumlertdacha et al., 1995. Lumlertdacha and Lovell, 1995). Increased Sa:So ratios in serum, liver, kidney and muscle, but not brain, were found at $\geq$10 mg FB_1/kg after 12 weeks (Goel et al., 1994)

One-year-old carp consuming pellets containing purified FB_1 at 0.5 and 5.0 mg FB_1/kg body weight for 42 days had dose-dependent clinicopathologic changes in serum indicating that liver (increased alanine and aspartate transaminase activities and bilirubin concentration) and kidney (increased creatinine concentration) were target organs (Pepeljnjak et al., 2003). Hematologic alterations were also observed. body weight decreased in both treatment groups and there was a higher incidence of bacterial dermatological lesions in the higher dose group caused by *Aeromonas salmonicida* subsp. *nova*. FB_1 served as a promoter for aflatoxin B_1 and *N*-methyl-*N*′-nitro-nitrosoguanidine (MNNG)-initiated liver tumors in rainbow trout (Carlson et al., 2001).

6.7. Diagnosis, treatment and prevention of toxicoses

Diagnosis is based on a history of ingestion of maize, particularly maize screenings or unscreened maize, together with characteristic clinical signs and lesions. Detection of fumonisins at approximately 10 ppm in horse feed or 50 ppm in pigs feed is highly suggestive of toxicosis. However, the feed sample presented for analysis is often from a subsequent batch of feed, not from the initial batch of feed responsible for toxicity. High pressure liquid chromatographic (HPLC) assays for fumonisins in feed are available at most veterinary diagnostic laboratories and an ELISA-based screening test for fumonisin is commercially available (Krska et al., 2007). Sa and So, considered excellent biomarkers of exposure, can be determined by HPLC in serum and frozen or formalin fixed tissues (liver and kidney being the most useful; Hsiao et al., 2007). However, the assay for Sa and So is currently only available in research laboratories and not on a routine diagnostic basis.

Since there is no known effective therapy, prevention of intoxication is of utmost importance. In this regard, strict adherence to the guidances for fumonisins in animal feeds and materials for use in feeds that have been issued by the USFDA (Table 1) and European Union Commission (Table 2) is important. The guidances vary by species according to their sensitivity to fumonisins, however, it is important to recognize that, in some cases, the margins of safety might be narrow. A possible strategy to prevent toxicoses is suggested by the finding that fumonisin B–glucose reaction products are less toxic when fed to pigs (Fernandez-Surumay et al., 2005). However, more studies are needed to determine the efficacy and commercial feasibility of using glucose supplementation or other physical–chemical methods (Humpf and Voss, 2004) to reduce fumonisins in maize used for animal feeds.

7. Conclusion

Since their discovery in 1988, fumonisins have been the subject of numerous toxicological investigations in laboratory and farm animals. Fumonisins, like the *Fusarium* species that produce them, are toxic to a wide range of laboratory and farm animal species and elicit a spectrum of toxicities that are likely mediated through mechanisms that involve disruption of sphingolipid metabolism and sphingolipid-mediated processes. Some diseases, like ELEM and PPE, are unique species-specific toxicoses while nephrotoxicity occurs in many species and hepatotoxicity in all species. Fumonisins have also been shown to exert various immunological and reproductive effects under experimental conditions, however, the extent to which such effects occur in farm animals and their impact on agricultural productivity and food safety are poorly understood. While various strategies are being pursued to develop methods to reduce fumonisins in maize or in maize-based animal feed products, the effectiveness and commercial feasibility of these methods remain to be demonstrated (Jouany, 2007). Therefore, awareness of the animal diseases associated with fumonisin exposure combined with reducing exposures through feed monitoring and adherence to appropriate USFDA or European Union guidances is important to minimize fumonisin-related diseases and production problems in animals.

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